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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,613	04/17/2001	John Joseph Hopwood	2249/104	9830

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,613	HOPWOOD ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-21,25-27,29-31 and 60-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21, 25-27, 29-31, 60-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-21-05 has been entered.

Claims 19-21, 25-27, 29-31, 60-64 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 5-25-05, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Applicant's amendment to the first line of the specification is acknowledged

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19-21, 25-27, 29-31, 60-64 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sasaki et al. (J. Biochem, 1991, Vol. 110:842-846). This rejection is based on the public availability of a printed publications reporting the purification of the above enzyme from various sources.

Claims 19-21, 25-27, 29-31, 60-64 of the instant application are drawn to a recombinant, α-N-glucosaminidase or a fragment of the same, expressed in mammalian cells, yeast or insect cells, wherein the mammalian cell is capable of N-glycosylating the enzyme, wherein the NAG enzyme is in a glycosylated form and has a molecular weight of at least 79kDa to 89kDa when determined by SDS/PAGE and wherein the amino acid sequence of the NAG is substantially the same as that of human NAG and wherein the amino acid sequence of said enzyme is as set forth in SEQ ID NO:2 or has at least 80% sequence identity to SEQ ID NO:2 and wherein the enzyme is produced by expression of a nucleic acid which encodes the enzyme or is complementary to a sequence encoding the enzyme and is carried in a vector capable of expression in a eukaryotic or prokaryotic cell, wherein the enzyme has an amino acid sequence that is 80% similar and encoded by a nucleic acid capable of hybridizing to SEQ ID NO:1 or 3 under high stringency conditions.

Sasaki et al. disclose the isolation and purification of the above enzyme. Sasaki et al. teach a 39,000 fold purification of a human α-N-acetylglucosaminidase (NAG) from human liver. The reference teaches that the enzyme is 80 kDa size when tested by SDS/PAGE as well as other characteristics of the enzyme. The reference also teaches that a deficiency of the above enzyme is known as MPS IIIB or Sanfilippo B syndrome a severe neurodegenerative disorder in

humans. However, the reference does not teach the recombinant form of the enzyme or a pharmaceutical composition comprising the enzyme. The reference does not disclose the amino acid sequence of the enzyme or the nucleotide encoding the enzyme as capable of hybridizing to SEQ ID NO:1 or 3 under high stringency conditions. However, Examiner takes the position that the enzyme disclosed in the reference and that claimed in the instant invention are inherently one and the same. Since the enzyme has been isolated from a source identical to that in the instant application, Examiner also takes the position that the glycosylation aspect, molecular weight and the amino acid sequence the nucleotide sequence which encodes the enzyme are all inherent characteristics and that the enzyme disclosed in the reference and that claimed are one and the same. Applicants have not done anything to said enzyme except to isolate the recombinant form of the purified enzyme in the reference. Examiner sees no material, structural or functional difference between the purified and the recombinant enzyme. Therefore, Examiner takes the position that Sasaki et al. anticipates claims 19-27, 29-31, 35-36, 60-64 as written based on inherency.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Or in the alternative, the teachings of Sasaki et al. combined with the common knowledge in the art regarding recombinant DNA technology renders the claims 19-21, 25-27,

29-31, 60-64 obvious for the following reasons. The reference not only provides a purified NAG enzyme but also clearly identifies the important role the enzyme plays in the inherited disease known as mucopolysaccharidosis IIIB. Using the purified enzyme provided in the above reference, it would have been obvious to those skilled in the art to obtain its amino acid sequence information by amino acid sequencing and isolate a cDNA clone from a cDNA library and the recombinant form of the enzyme or as a fusion protein fused to an affinity tag and expressed in any of the host cells including insect cells or CHO cells using the isolated cDNA in a vector as is well known in the art. Using such recombinant enzyme it would also have been obvious to those skilled in the art to make pharmaceutical compositions comprising the enzyme for treating the deficiency disorder. One of ordinary skill in the art would have been motivated to do so because a purified protein can be made in large amounts when obtained in the recombinant form. Furthermore, as the above reference teaches that a deficiency of the above enzyme leads to MPS IIIB disorder, it would have been obvious to those skilled in the art to provide the recombinant enzyme as a pharmaceutical composition for enzyme replacement therapy to those affected by the above disorder. One of ordinary skill in the art would have a reasonable expectation of success since the above reference provides the purified enzyme and also teaches its role in MPS IIIB disorder and the art provides the methods to make a recombinant protein or a pharmaceutical composition comprising the same.

Therefore, Sasaki et al. render the above invention *prima facie* obvious to those skilled in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing at length.

Previously, applicants argued that the instant invention can be distinguished from that of the reference on the following lines a) source of the enzyme, b) molecular weight of the enzyme. In response to the obviousness part of the rejection, applicant argued that "in a rejection of product or composition claims for obviousness, the issue is "the obviousness of the claimed compositions, not of the method by which they are made" and that the reference does not provide either the amino acid sequences or the nucleotide sequences.

Examiner respectfully disagreed with the above arguments and reiterated that the source of reference enzyme and that of the instant invention is one and the same, and that is humans, and that applicant's conclusion that the enzyme from the liver would be different from the enzyme isolated from placenta or leukocytes is highly misplaced, unless they can provide a reference to show the same and that without such a reference there is no scientific reason to believe that the enzymes from different organs of the same organism would be different. With respect to the applicant's argument regarding the molecular weight Examiner maintained that the difference in the molecular weights between the claimed enzyme and that in the reference is not significant and even could be due to experimental error and therefore based on that it cannot be accepted that the two enzymes are different. Next Examiner reminded applicants that his rejection is based on "inherency" and therefore, the requirement that the reference must disclose the amino acid sequence does not apply. Examiner also argued that characteristics such as amino acid sequence and other physical characteristics are inherent to a given protein or the enzyme and that applicants have not done anything except to obtain a purified protein as a recombinant protein. Examiner maintained that applicants have not shown a material, structural or functional difference/s between the purified enzyme and the recombinant enzyme and absent

such information, the purified protein inherently possesses all the characteristics of the recombinant enzyme even though the reference is not explicit about those characteristics.

In response to applicant's argument that the reference polypeptide and the claimed polypeptide are not one and the same based on the teachings of Weber et al. research article Examiner noted that the reproduced paragraphs from Weber et al. only describe the differences between the two forms of NAGLU, the 77 and 80kDa and is totally silent between the differences one can see in the purified form and the recombinant form of the enzyme and that while the reference of Weber et al. indicates that the difference between the 79 and 89 kDa proteins is due to glycosylation, it does not indicate whether such differences exist between the purified enzyme and the recombinant enzyme.

Now, under the remarks section of the paper filed on 9-23-05, applicants argue that Examiner has erred in taking such a position and point to page 257 of the Weber et al. reference which states:

> Although the glycosylation pattern of rNAGLU seems to be slightly different when compared to enzyme purified from placenta, other characteristics are identical. Since the glycosylation is crucial for the phosphorylation we cannot exclude that the altered pattern is causing the weak dephosphorylation of the recombinant enzyme while the native enzyme is phosphorylated to the same extent as other lysosomal enzymes."

Applicants now argue that they have clearly shown that the presently claimed invention is distinct from a tissue-derived source of enzyme such as that described in (Weber et al. ???) and even Sasaki et al. (1991) J Biochem. 274245):842-846 (upon which the rejection under 35 U.S.C. 102(b) is based).

While applicant's arguments appear to be persuasive (and perhaps meant to say such as that described in Sasaki et al. as opposed to Weber et al. and Sasaki et al.), Examiner has continued to maintain the above rejection because, applicants have not amended the claims to describe the structural differences between their recombinantly produced enzyme and the naturally occurring enzyme. If applicants are indeed arguing that the purified enzyme is structurally different from recombinant enzyme, said structural differences are not reflected in the claimed polypeptide. Claims continue to be directed to a polypeptide comprising the characteristics of a purified protein. Examiner suggests that either applicants cancel all the claims or amend the claims to reflect the structural changes that they allege between the recombinant and the purified enzyme provided they have ample support in the specification to make such amendments. Furthermore, the above rejection is maintained since applicants have not shown that it is necessarily true that all recombinantly produced enzyme has the structure which theirs has.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306/9307 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

December 19, 2005